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Clinical trials in ovarian carcinoma: requirements for standard approaches and regimens

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The 3rd International Ovarian Cancer Consensus Conference (OCCC), held 3–5 September 2004, in Baden-Baden, Germany, addressed 12 questions critical to the future directions of clinical research into the treatment of newly diagnosed ovarian cancer. Four of these questions examined issues related to the current standard of care and to what should, for now, constitute a proper control arm in future phase III clinical trials. These questions are listed in Table 1.

Consensus on the answer to these four questions is crucial to the interpretation of major clinical trials. Such a consensus will encourage the use of similar standards in each major trial and thus will provide a common basis for interpretation. This article will provide a detailed discussion of the rationale for the unanimous consensus achieved for each of these four questions.

Surgery in trials of newly diagnosed patients

The first question asks simply whether there is a need to define strictly the extent and type of surgery for patients in first-line trials. Divergent approaches to surgical requirements in recently reported major trials prompted this question. For example, in the major trials examining the inclusion of a taxane in front-line trials, quite different approaches to surgical requirements are apparent. The two Gynecologic Oncology Group trials (GOG protocols 111 [1] and 132 [2]) conducted in the USA employed strict definitions for the extent and type of surgery and required accurate surgical staging as well as an aggressive attempt at surgical bulk reduction. At the other extreme, the Medical Research Council (MRC) trial, ICON3 [3], did not mandate formal FIGO surgical staging. Although stage was reported, one cannot assume accurate surgical staging in the absence of a formal requirement. The remaining trial, the European–Canadian OV-10 study [4], had requirements closer to the GOG approach than to the MRC approach.

That such divergent surgical approaches can result in very different outcomes is best illustrated by the apparently contradictory results of two large trials of interval surgical cytoreduction [5, 6]. The first of these two trials conducted by the EORTC in Europe randomized patients with advanced ovarian carcinoma who had been deemed not amenable to surgical cytoreduction by the initial surgeon to either six cycles of cyclophosphamide plus cisplatin or to three cycles of the same chemotherapy followed by an interval attempt at surgical cytoreduction followed by three more cycles of the same chemotherapy [5]. The results suggested a progression-free and overall survival advantage for those patients assigned to interval surgical cytoreduction. The second study conducted by the GOG in the USA randomized a similar group of patients to either six cycles of paclitaxel plus cisplatin or three cycles of paclitaxel/cisplatin followed by interval surgical cytoreduction followed by three more cycles of paclitaxel/cisplatin [6]. In contrast to the EORTC trial, the GOG trial showed no advantage for those patients assigned to the interval debulking. The key to the proper interpretation of these two trials lies in the aggressiveness of the initial attempt at surgical cytoreduction prior to study entry. In the EORTC study, patients were seen by a variety of surgeons, most of whom had not received formal training in surgical bulk reduction and only interval debulking was centralized. Patients entering the GOG trial were, for the most part, seen by trained gynecologic oncologists. Each underwent a very aggressive attempt at surgical bulk reduction if at all possible. The nature of the initial surgery thus determined whether interval surgical bulk reduction resulted in patient benefit, and the two trials actually do not contradict each other. The data from these two studies argue for the necessity of strict surgical entry criteria as a part of randomized trials of ovarian carcinoma since differences in the initial surgery can impact outcomes and alter conclusions from the trial.

These considerations led to the unanimous answer that there is a need to define strictly the extent and type of surgery for patients in front-line trials. The basis for this conclusion was three-fold. First, clinical trials investigating the management of celomic epithelial carcinoma of the ovary and peritoneal cavity, the target population of essentially all major trials of 'ovarian cancer', should ensure that only patients with this diagnosis, not those with gastrointestinal malignancies or ovarian tumors of low malignant potential, are included [7–9]. Secondly, results of therapy in any given trial depend to a great degree on the composition of the study population with regard to stage or

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Table 1. Consensus questions addressing standard approaches and regimens

1. Is there a need to strictly define the extent and type of surgery for patients in first-line trials?
2. What is the impact of post-recurrence/progression treatment on the end points of first-line therapy? Do we need to standardize post-recurrence/ progression therapy or, if not, how can we assess its survival impact?
3. Do we need a common 'GCIG recommended/accepted' standard arm for comparison with any new regimen/approach in first-line trials?
4. Which regimen/kind of regimens can be regarded as standard comparator for future first-line trials?

Table 2. Consensus statements in response to question 1

Is there a need to strictly define the extent and type of surgery for patients in first-line trials?
1. Tissue should be obtained for histopathologic diagnosis to confirm the presence of primary ovarian or peritoneal carcinoma.
2. Staging should be performed according to FIGO guidelines. For example, this includes at least lymph node sampling and peritoneal staging in early stage invasive disease (FIGO I–IIA).
3. Up-front maximal surgical effort at cytoreduction with the goal of no residual disease should be undertaken.
4. When cytoreductive surgery is not possible initially, it should be considered in patients who do not have progressive disease after three to five cycles of chemotherapy.
5. Patients with ovarian cancer should have their surgery performed by an appropriately trained surgeon with experience in the management of ovarian cancer.

extent of disease [10]. Thirdly, volume of disease, particularly in patients with FIGO stage III disease, impacts on response to chemotherapy and survival [11–14]. To interpret properly results of a clinical trial of patients with newly diagnosed celomic epithelial carcinoma, one must know that patients in the trial actually had celomic epithelial carcinoma and that the arms of the study are balanced with regard to stage and volume of residual disease. Only if the study adequately addresses each of the above considerations will accurate interpretation be possible.

These considerations then led to further discussion as to what should be the minimum surgical standard in a well-designed clinical trial. The consensus adopted five criteria for minimum surgical standards that should be incorporated into each clinical trial, which are listed in Table 2.

The first point answers the requirement that a properly designed study should insure that patients included actually have the disease under study. This requires histology rather than just the triad of positive cytology, high CA 125 and a pelvic mass. Tissue may be obtained at laparoscopy or laparotomy. This is particularly important to eliminate those patients who have either an ovarian tumor of low malignant potential or a gastrointestinal malignancy with peritoneal carcinomatosis.

The second point addresses the need for accurate surgical staging. FIGO guidelines define the information needed to determine the surgical stage [10]. The staging procedure should be planned to elicit all needed information. This includes at least omentectomy, cytology, lymph node sampling and multiple peritoneal biopsies in those patients who have no gross disease beyond the ovary and hence appear to have stage I disease. Accurate staging is important not only because stage is an important determinant of survival independent of treatment and thus impacts study end points, but also because the extent of disease at diagnosis might reflect differences in biology and may impact on the likelihood of response to systemic therapy.

The third and fourth points concern the importance of a maximum surgical effort. The rationale cited for surgical cytoreduction in ovarian carcinoma is two-fold: removal of resistant clones of cells and removal of large masses that may be poorly vascularized and thus may not be amenable to delivery of adequate drug to all cells in the mass [15]. If the stated rationale for surgical cytoreduction is correct, then initial bulk reduction prior to systemic therapy makes far better sense than does debulking after some or all of the systemic therapy has been delivered; hence, point three cites the desirability of an initial maximal effort at surgical cytoreduction. That one attempt at a maximal surgical effort is important is supported by the results of two previously described studies of interval surgical debulking. The European study [5] included mostly patients who had not had a maximum surgical effort initially and demonstrated a significant survival benefit for interval debulking after three of six cycles of chemotherapy had been delivered. The GOG trial [6] in the USA included mostly patients who had undergone a maximal surgical effort initially without achieving the status of minimal residual disease. This study showed no advantage for interval debulking after three cycles of chemotherapy. Taken together, these two trials suggest an advantage for maximal surgical debulking but only in those patients who have not already undergone such an effort. Based on the rationale for surgical cytoreduction stated above, interval surgical debulking should be reserved for those patients who, for some reason, cannot undergo initial maximum effort for surgical cytoreduction. In studies to date, interval debulking has most commonly been performed after three cycles of therapy [5, 6]. There are no data that define this as the optimal timing; hence, the consensus statement leaves this to the discretion of the investigator who is designing the trial.

The fifth point expresses the unanimous opinion that a maximal surgical effort requires a surgeon who has extensive experience with debulking surgery. Several studies establish the value of the surgical cytoreduction being carried out by a surgeon well-trained in the procedure in terms of both overall survival and the frequency with which the disease can be reduced to small-volume residual disease [16–22]. Experienced surgeons achieve a small-volume residual state more often, and patients achieving small-volume residual disease experience a longer survival. It is important in clinical trials that patients receive similar surgery since the quality of that surgery will determine the accuracy of surgical staging and the adequacy of surgical debulking, both of which may impact on patient outcome and thus potentially skew study results if not applied uniformly.

In summary, surgery in clinical trials should be applied uniformly to the entire study population in accordance with strict

definitions for diagnosis, staging and bulk reduction. The five consensus points define the minimum standards for achievement of this conclusion.

Post-recurrence/progression therapy

The second question focuses on the impact of post-recurrence/progression treatment on the end points of first-line therapy: what is the impact of post-recurrence/progression treatment on the end points of first-line therapy? Do we need to standardize post-recurrence/progression therapy or, if not, how can we assess its survival impact? In response to this three-part question, four points comprise the unanimous consensus, as listed in Table 3.

The first point addresses the first part of the question, which asks whether there is such an effect. The unanimous answer to this first part of the question is that there is in fact an impact on overall survival. One need look no further than the publication of the results of the ICON4/AGO-OVAR-2.2 trial [23] to see such an impact. In this study, patients with platinum-sensitive recurrent disease were randomized to either a platinum regimen without a taxane or a platinum regimen with a taxane. Those receiving a taxane/platinum regimen experienced an improvement in progression-free and overall survival. In addition to the platinums and the taxanes, a plethora of agents such as pegylated liposomal doxorubicin, topotecan, oral etoposide and gemcitabine, among others, have demonstrated activity in recurrent or persistent ovarian carcinoma and may impact on survival as post-recurrence/progression therapy. In particular, pegylated liposomal doxorubicin, in a randomized phase III trial, produced both a progression-free survival advantage and an overall survival advantage over topotecan in the subgroup of patients who were platinum sensitive [24].

The second point responds to the second part of this question, which asks whether it is feasible to standardize post-recurrence/progression therapy. Standardization would distribute the effect of post-recurrence/progression therapy uniformly among the arms of front-line trials and thus account for the potential confounding effect of such therapy on survival as an end point of front-line trials. In essence, a front-line trial would define not only front-line therapy, but all subsequent therapy that would be given on recurrence or progression. Such therapy would, of necessity, have to be the same for all patients regardless of front-line therapy so that any effect would thus be uniform among the arms. For example, in a trial of paclitaxel/carboplatin versus carboplatin, patients in the carboplatin arm would never receive paclitaxel but rather would receive the same second and subsequent line therapy as that given to patients who were treated initially with paclitaxel/carboplatin. The unanimous answer to this part of the question is that, at least at the current time, such standardization is neither feasible nor necessarily desirable for at least two reasons. First, if for no other reason, it would be impossible to deny a portion of the patient population the potential benefit of certain active agents that might be excluded in this attempt to standardize post-recurrence/progression therapy. Secondly, a superior first-line therapy might produce more patients categorized as platinum sensitive. This at the very least might make the impact of post-recurrence/progression therapy different in each arm, and it could necessitate the use of very different post-recurrence/progression therapy in each arm.

Since standardization of post-recurrence/progression is not feasible, the third point addresses the crucial third part of the question. How can we assess the survival impact of post-recurrence/progression therapy? The short answer is that we cannot. An example of this phenomenon is GOG protocol 132 [2], which randomized patients with large-volume residual stage III–IV ovarian carcinoma to either cisplatin or paclitaxel or the concurrent administration of both agents. Despite the previously positive findings of GOG protocol 111 [1], which demonstrated superiority of paclitaxel/cisplatin over cyclophosphamide/cisplatin with regard to overall survival as well as response rate and progression-free survival, GOG protocol 132 showed no differences between cisplatin and paclitaxel/cisplatin and no differences in overall survival between paclitaxel and paclitaxel/cisplatin. At first glance, these results appear to contradict the results of GOG protocol 111. This contradiction, however, relates to the fact that essentially every patient completing cisplatin with residual disease then received paclitaxel prior to progression in violation of protocol requirements. The study in reality rather compared sequential versus concurrent cisplatin plus paclitaxel and demonstrates that 'second-line therapy' can in fact obscure a survival advantage associated with the addition of a new agent to front-line therapy. Despite this, this study has been cited as evidence that the use of a taxane as a part of front-line therapy is not necessary.

In the absence of the ability to account for the impact of post-recurrence/progression therapy, the position that survival is the gold-standard end point and should be the primary end point for all major trials is dangerous. Even with currently available agents, post-recurrence/progression therapy can obscure a survival advantage for the addition of new agents to front-line therapy. As the efficacy of post-recurrence/progression therapy continues to improve with the addition of more new agents to the therapeutic armamentarium, this danger will grow and confound attempts to improve on front-line treatment.

The only solution that remains is to identify new primary end points that are not impacted by post-recurrence/progression therapy. The obvious and best candidate is progression-free

Table 3. Consensus statements in response to question 2

What is the impact of post-recurrence/progression treatment on the end points of first-line therapy? Do we need to standardize post-recurrence/progression therapy, or if not, how can we assess its impact on survival?
1. There is an impact of post-recurrence/progression therapy on overall survival.
2. It is not possible to standardize post-recurrence/progression therapy at the present time.
3. Although overall survival is an important end point, progression-free survival may be the preferred primary end point for trials assessing the impact of first-line therapy because of the confounding effect of the post-recurrence/progression therapy on overall survival. When progression-free survival is the primary end point, measures should be taken to protect the validity of analysis of overall survival.
4. There should be clear definition of how to determine progression-free survival.

survival. This end point has the advantage of having been reached before the introduction of additional therapy provided that the study specifically prohibits additional treatment before progression and strictly enforces that prohibition. The consensus concluded that progression-free survival may be the best primary end point, but members felt that the study design should take measures to insure that a valid analysis of overall survival can also be conducted.

These considerations lead to the fourth point, which concerns the importance of insuring an appropriate determination of progression-free survival. Patients must be followed in exactly the same way. Intervals between assessments for progression must be determined prospectively and must be the same for all patients. The assessments must be strictly defined with key examinations and tests such as the serum CA 125 and scans performed at predefined, identical intervals for all patients. Criteria for progression must be set and followed assiduously. Follow-up intervals must take into account the median progression-free survival observed in prior studies and must be set at intervals short enough to avoid artificial alteration of the observed progression-free interval. For example, both ICON4/AGO-OVAR-2.2 [23] and the AGO-OVAR/NCIC/EORTC trial of gemcitabine/carboplatin [25] reported median differences in progression-free survival of approximately 3 months; hence, follow-up intervals of longer than 3 months might artificially alter the observed progression-free survival in platinum-sensitive patients. Such measures protect against artificial differences in progression-free survival resultant from variations in the timing and content of follow-up tests and inappropriate follow-up intervals in the approach to patient reassessment.

In conclusion, post-recurrence/progression therapy can clearly impact what has been the traditional primary end point, survival. Standardization of post-recurrence/progression therapy as a means for accounting for this impact is not currently feasible. The only practical approach is to adopt an alternative primary end point that is not impacted by post-recurrence/progression therapy. The consensus is that progression-free survival appropriately and strictly defined may be the best alternative end point and that, in those studies that choose this alternative primary end point, the design of the trial must protect the validity of an analysis of survival as well.

Standard comparator regimen

The third and fourth questions ask whether the Gynecologic Cancer Intergroup (GCIG), as represented by the participants in the OCCC, should recommend a particular regimen as the standard against which new regimens and approaches should be compared and whether the OCCC could identify the regimen that should be recommended. In response to the first of these two questions, the point listed in Table 4 was adopted unanimously.

The rationale for this statement is that, if agreement can be reached as to what constitutes the standard of care worldwide for the use of systemic therapy in ovarian carcinoma, acceptance of any new regimen as advantageous would depend on the demonstration of superiority for the new regimen over the standard of care. For example, demonstrating that a new regimen is superior to melphalan, the standard of care in the 1970s, would hardly be regarded as evidence that the new regimen was superior to a platinum-based regimen that represented the standard of care in the late 1980s. Allowance of 'variations' means that regimens other than the standard are allowed for defined and compelling reasons that are clearly stated and supported by appropriately cited literature. However, this option ('variations') should not be misinterpreted as allowing suboptimal regimens such as melphalan to be considered as standard comparator.

Table 4. Consensus statements in response to question 3

Do we need a common 'GCIG recommended/accepted' standard arm for comparison with any new regimen/approach in first-line trials?
1. There should be a common 'GCIG recommended/accepted' standard arm for comparison with any new regimen/approach. Variations are allowed for clearly defined reasons.[a]

[a]Regimens other than the standard are allowed for clearly defined and compelling reasons that are clearly stated and supported by appropriately cited literature. However, this option ('variations') should not be misinterpreted as allowing suboptimal regimens to be considered as standard comparator.

Given that the answer to question three was unanimously affirmative, question four then became relevant. If there is consensus that a standard comparator regimen should be recommended, then what is that regimen or kind of regimen? In response to this question, participants unanimously approved four points, as listed in Table 5.

The first point represents the results of a debate between two currently employed approaches to large trials in ovarian cancer as illustrated by the ICON4/AGO-OVAR-2.2 trial [23] and the AGO-OVAR/NCIC/EORTC trial of carboplatin with or without gemcitabine [25]. One approach is illustrated by ICON4/AGO-OVAR 2.2 [23]. In this trial, 802 patients with platinum-sensitive recurrent ovarian carcinoma were randomized to receive either a platinum-based regimen without a taxane or a taxane/platinum regimen. Specific agents, doses and schedules were not specified. In each arm, a variety of regimens were employed. For example, those assigned to a platinum-based regimen without a taxane received carboplatin alone (71%), CAP (cyclophosphamide/doxorubicin/cisplatin, 18%) or a variety of other regimens without a taxane (12%). Those assigned to a taxane/platinum regimen received paclitaxel/carboplatin (81%), paclitaxel/cisplatin (10%), paclitaxel/carboplatin/cisplatin (5%) or a variety of other taxane/platinum regimens (4%). Dose and schedule within each regimen also varied, as did history of prior treatment and tumor characteristics (e.g. presence of measurable, evaluable or surgically completely removed disease). Although such an approach may be valid, the majority of conference participants expressed their preference for a more uniform protocol than the pragmatic approach adopted in ICON4 (this preference led to an unanimous decision for strictly defined comparator regimens for first-line trials – see statement 3.1).

The alternative approach is illustrated by the results of another GCIG trial (AGO-OVAR/NCIC/EORTC) [25] presented at the 2004 meeting of the American Society of Clinical Oncology.

Table 5. Consensus statements in response to question 4

Which regimen/kind of regimens can be regarded as standard comparator for future first-line trials?
1. Within a given trial the chemotherapy regimen should be standardized and consistent with respect to drugs, dose and schedule.
2. The recommended standard comparator for trials on medical treatment in advanced ovarian cancer (FIGO IIB–IV) is carboplatin/paclitaxel.
3. The recommended regimen is carboplatin with a dose of AUC 5–7.5 and paclitaxel 175 mg/m^2/3 h given every 3 weeks for six courses.
4. The recommended standard in early stage ovarian cancer (FIGO I–IIA) patients in whom adjuvant chemotherapy is indicated should contain at least carboplatin AUC 5–7.5.

In this trial, patients with platinum-sensitive recurrent ovarian carcinoma were randomized to either carboplatin AUC 5 intravenously or gemcitabine 800 mg/m^2 intravenously on days 1 and 8 plus carboplatin AUC 4 intravenously on day 1 with both regimens repeated every 3 weeks. Furthermore, patient selection with respect to prior treatment and tumor characteristics was specified. This trial was powered for progression-free survival as the primary end point and demonstrated superiority for the gemcitabine/carboplatin combination at the expense of increased myelosuppression, which did not translate into an increase in febrile neutropenia. This trial, by minimizing potentially confounding variables, draws a credible conclusion that gemcitabine plus carboplatin is superior to carboplatin alone.

The unanimous consensus of conference participants is that the approach to employ defined regimens represents the preferred approach. By defined regimen, the consensus means that regimens should be defined as to specific agents as well as doses and schedules. The rationale for this position is that such an approach provides a clearer result by eliminating many potentially confounding variables and still permits adequate accrual to complete study objectives.

The second point presents paclitaxel plus carboplatin as the regimen best supported as the standard comparator by current data. Two large trials, GOG protocol 111 [1] and the European–Canadian trial OV10 [4], demonstrated superiority of paclitaxel/cisplatin over cyclophosphamide/cisplatin with regard to response rate, progression-free survival and overall survival. Two subsequent large trials [26, 27] then showed no significant differences in efficacy between paclitaxel/cisplatin and paclitaxel/carboplatin, and also noted an advantage for paclitaxel/carboplatin in terms of ease of administration, decrease in toxicity and improvement in quality of life. Two large trials, GOG protocol 132 [2] and ICON3 [3], purport to contradict the reported value of the addition of paclitaxel to a platinum compound; but these two trials exhibit problems in design or execution that adversely impact their credibility. GOG protocol 132 purported to compare single-agent cisplatin versus single-agent paclitaxel versus the combination of paclitaxel plus cisplatin; however, almost half of the patients on the two single-agent arms were treated in violation of protocol requirements with the other agent as second-line therapy before progression occurred. ICON3 included all stages of disease and permitted two different control regimens. This unnecessarily adds two potentially confounding variables and makes clear interpretation of the results problematic. The weight of evidence thus favors paclitaxel/carboplatin as the standard comparator regimen. This weight of evidence effectively means that demonstration of superiority for a new regimen over an alternative control regimen such as single-agent carboplatin would hardly be accepted as establishing a new standard of care unless the new regimen had been shown to be superior to paclitaxel/carboplatin.

The third point addresses the specifics of the standard regimen. The use of paclitaxel at a dose of 175 mg/m^2 is supported by a meta-analysis [28], two randomized trials of various paclitaxel doses [29, 30] and the toxicity of paclitaxel at various dose levels. The meta-analysis suggests that response rate to paclitaxel increases up to a dose of 175 mg/m^2, but further dose escalation results in a decrement in response rate. The two randomized trials of dose showed a small increase in response rate as dose goes from 135 to 175 mg/m^2 and again as dose goes from 175 to 250 mg/m^2; but escalation of dose above 175 mg/m^2 results in a major increase in neurotoxicity, a major problem for any attempt to combine paclitaxel with carboplatin. These considerations support the use of paclitaxel at a dose of 175 mg/m^2.

The recommendation of carboplatin at an AUC that ranges from AUC 5 to 7.5 reflects what has been used in clinical trials to date. The optimal dose is not known. There is, however, one consideration which should be taken into account when deciding on the dose of carboplatin. Paclitaxel and carboplatin interact in such a way that myelosuppression is markedly reduced when the two are used together [31]. The mechanism for this interaction is not known; hence, it is also not known whether the interaction interferes in any way with the antitumor effect of the drugs. Studies by the German group, AGO-OVAR, suggest that there is no impact on antitumor effect across a range from an AUC of 5 to an AUC of 6 (A. du Bois, personal communication). The two large studies of paclitaxel/cisplatin versus paclitaxel/carboplatin, however, present some interesting trends. In the AGO-OVAR trial [26], which employed an AUC of 6, the hazard ratio for survival was 1.05, a small and statistically insignificant trend favoring paclitaxel/cisplatin when the whole study population was considered. However, the hazard ratio was 0.9 in the planned stratified analysis in the optimally debulked population, a small but insignificant trend in favor of the carboplatin combination. In the GOG trial [27], which employed an AUC of 7.5, the hazard ratio for survival was 0.84, a larger but still statistically insignificant trend favoring paclitaxel/carboplatin. This trial included only optimally debulked patients. These data suggest neither that carboplatin is superior to cisplatin nor that the higher AUC may offer some advantage in optimally debulked patients. Because these considerations do not provide a clear answer to the optimal AUC of carboplatin, the consensus left the dose of carboplatin flexible across the range of AUC 5–7.5. A meta-analysis of the data on this issue of carboplatin dose is planned by the AGO-OVAR and GOG in the near future (A. du Bois, personal communication).

The remaining two components of the standard regimen involve the number of cycles of therapy and the interval between treatments. Although participants concede that the optimal number of cycles has not been determined, unanimous opinion

recommends six cycles as the standard. This is based on two randomized but underpowered trials [32, 33] that showed no clear advantage for more than five to six cycles and also on common usage for almost a decade. In addition to rather low numbers, a considerable portion of the enrolled patients did not receive cycle numbers as planned. Only one recent trial employed a number other than six cycles, and that is the just completed study of paclitaxel/carboplatin versus two triplets (adding either gemcitabine or pegylated liposomal doxorubicin) versus two sequential doublets (either gemcitabine/carboplatin or topotecan/carboplatin followed by paclitaxel/carboplatin). Eight cycles of each regimen were used in this study, but the rationale involved the two regimens evaluating sequential doublets. Many potential participants were concerned about patients assigned to these two regimens receiving only three cycles of paclitaxel/carboplatin; hence, in order to maintain a similar treatment duration, each arm of the study called for eight cycles of therapy. Patients receiving sequential doublets thus received four cycles of the new doublet followed by four cycles of paclitaxel/carboplatin. Because of the reason for using eight cycles, this trial did not impact on the recommendation of six cycles as standard. It did, however, prompt the addition of the caveat that variation from the recommended standard comparator should be permitted for a valid reason (Table 4).

The recommended interval between treatment cycles is 3 weeks. The rationale for this recommendation is the observation that, in patients who receive a paclitaxel/carboplatin combination, recovery from dose-limiting myelosuppression is usually complete at 3 weeks rather than the 4 weeks usually seen with carboplatin not in combination with paclitaxel. All trials using the standard regimen to date have employed the 3-week interval.

Taken together, these three points recommend a standard comparator regimen for all randomized trials of advanced ovarian carcinoma that consists of paclitaxel 175 mg/m^2 over 3 h plus carboplatin AUC 5–7.5 every 3 weeks for six cycles. Deviation from this standard comparator regimen should only be for a clear and valid reason.

The fourth point recognizes the limited amount of data available for patients with limited disease (stages I–IIA) at high risk for recurrence. Two studies provide a rationale for the use of adjuvant chemotherapy at least in those with disease at high-risk for recurrence (high-grade disease, implants on the surface of the ovary, disease outside the ovary, positive peritoneal cytology or ascites): an Italian trial [34] and a combined analysis of ICON1 and the ACTION trial from Europe [35]. These studies suggest that high-risk patients experience a reduction in recurrence rate, an improvement in disease-free survival, and, in the case of the ICON1/ACTION trials, improved survival when treated with platinum-based chemotherapy. There are no randomized trials that address the value of adding paclitaxel to platinum in these patients. The resultant recommendation is that the standard comparator regimen be defined as a regimen that at least employs carboplatin at an appropriate AUC between 5 and 7.5. The higher dose should be considered only in those patients receiving a paclitaxel/carboplatin combination; and the issues raised in the foregoing discussion about carboplatin dose in patients with advanced disease should be considered.

Conclusions

The recommendations for standards for design and execution of major randomized trials in ovarian carcinoma are unanimous and reflect a common worldwide understanding of the weight of evidence. Philosophically, the thrust of these recommendations favors strict definition of entry criteria, strict requirements for the use of treatment modalities and end points that avoid the confounding impact of rapidly improving post-recurrence/progression therapy. Specifically, the recommendations call for unequivocal diagnosis, accurate staging, aggressive surgical bulk reduction, comparisons against paclitaxel/carboplatin as the standard of care at least in advanced disease, and avoidance of confounding influences of therapy subsequent to the study by the use of an end point (progression-free survival strictly defined and assessed) that is reached before further therapy is given. These recommendations form the foundation on which future randomized trials in ovarian carcinoma will be built.

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